MICROORGANISMS AND PSORIASIS

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It has been suggested previously that psoriasis is best explained as a distinctive inflammatory response to a variety of microbial stimuli, all acting primarily through activation of the alternative complement pathway. For the past several years we have conducted a "Problem Psoriasis Clinic" based on that premise. Patients are questioned, examined, and subjected to microbiologic laboratory investigations in an attempt to identify possibly relevant microorganisms, and then are treated with antibiotics. This article lists the most commonly found microorganisms in psoriasis patients and describes the usual treatment for each. Results obtained with this approach compare favorably with those achieved with more usual antipsoriasis treatments. We recommend that a microbiologic investigation and a trial of antimicrobial treatment should precede any plan to treat psoriasis patients with anything more than the simplest topical agents. (*J Natl Med Assoc.* 1994;86:305-310.)

Key words • psoriasis • dermatologic disease • seborrheic dermatitis

Noah's report of microbiologic findings of psoriasis patients subjected to a reasonably standardized range of investigations showed a relatively small list of frequently encountered organisms[1] (Table). Of interest is the fact that of these organisms, the two yeasts, the streptococci and the gram-negative rods, share the defect of being relatively incapable of eluding the alternate pathway activation of complement. Belew et al[2] had suggested previously that the alternative pathway activation of complement by *Malassezia ovalis* might explain how that organism could evoke an inflammatory response in seborrheic dermatitis despite the inconsistent evidence of humoral or cellular immune response. Subsequent studies[3-9] have shown evidence also of alternative pathway activation of complement in association with psoriasis. The recent report that the epidermis seems capable itself of producing factor B of the alternative pathway adds further support to these findings.[10]

Additional support for a possible causative role of microorganisms in psoriasis is the frequent association of such organisms with the closely related disorders of Reiter's syndrome, psoriatic arthritis, spondyloarthritis, osteitis, uveitis, and inflammatory bowel disease.[11] These associations and mechanisms have by no means yet been clearly defined but have received much more attention in their respective disciplines than they have by dermatologists. By far the most suggestive of such support, however, comes from seborrheic dermatitis, a condition that shares not only an often indistinguishable clinical but also a microscopic appearance with psoriasis, and is clearly evoked by the presence of *Malassezia*.[12]

The organisms that are likely to be of importance in patients with psoriasis include:

- *Malassezia ovalis* (*Pityrosporum ovalis*),
- *Candida albicans*,
- group A beta-hemolytic streptococci,
- group B beta-hemolytic streptococci,
- *Enterococcus faecalis* (*Streptococcus faecalis*),
- *Pseudomonas* species,
- *Klebsiella* species, and
- *Bacillus cereus*.

MALASSEZIA OVALIS

Malassezia ovalis is the accepted name now used in *Index Medicus* for the organism that for many years was

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TABLE. MOST FREQUENTLY ENCOUNTERED POTENTIAL PATHOGENS IN 297 PATIENTS WITH PSORIASIS*†

Organism	No. Isolates
Group A hemolytic streptococci	9
Group B beta-hemolytic streptococci	121
Group D beta-hemolytic streptococci	55
Group G beta-hemolytic streptococci	21
Klebsiella species	27
Escherichia coli	88
Enterobacter species	17
Proteus species	37
Pseudomonas species	20
Acinetobacter species	16
Bacillus species	49
Candida species (predominantly albicans)	67

*From reference 1.
†Heavy scalp colonization of *Malassezia* occurred in the majority of the scalp psoriasis patients seen in our clinic but were not tabulated in this study. Moreover, approximately one half of the patients showed elevations to one or more antigroup A streptococcal extracellular enzymes.

familiar to dermatologists as *Pityrosporum ovale.* Its role in the cause of seborrheic dermatitis has been championed over the years by Sabouraud,[13] Unna,[14] Moore et al,[15] Brotherton,[16] Brunnetiere et al,[17] and Farr and Shuster.[18] Its first description, however, was by Rivolta in 1873.[19] He discovered the unmistakable budding yeast in a red, scaly patch on his own cheek and named the organism *Cryptococcus psoriasis.* Controversy about its importance in seborrheic dermatitis persisted until recently but has now receded following the demonstration that when ketoconazole suppresses the growth of this yeast, the disease disappears.[20]

Our studies of seborrheic-area psoriasis show a high correlation with the presence of *Malassezia.* In preliminary open[21] and controlled[22] studies, ketoconazole seems to be effective in clearing scalp and face psoriasis. The related bifonazole was found to help "sebopsoriasis,"[23] and there is a recent report that dilute concentrations of anthralin also exert an imidazole-like effect on *Malassezia.*[24]

Applications of heat-killed *M ovalis* to unbroken and nontraumatized forearm skin evoked the appearance of psoriasis papules in persons with psoriasis but not in control subjects.[25] An animal model that both looks[26] and behaves[27] like psoriasis can be produced similarly with heat-killed *M ovalis.* We presently are involved in a large controlled study of ketoconazole in scalp psoriasis.

In addition to its usual presence in areas of seborrheic-distribution psoriasis, *Malassezia* also has been found in follicular-centered psoriasis on the arms and upper trunk. This pattern is difficult to differentiate from the familiar guttate psoriasis; it also seems to respond to treatment with ketoconazole.

CANDIDA ALBICANS

Candida albicans has been found regularly in association with diaper-area psoriasis.[28-33] Wachoviak et al[34] reported an increased presence of *Candida* in the stools of patients with psoriasis compared with control subjects. Hanel et al[35] found elevations in phospholipase A activity of *C albicans* strains isolated from the intestine of psoriatic patients. Duvic et al[36] reported an interesting psoriasiform eruption of the palms and soles in six of 20 patients with acquired immunodeficiency syndrome who were being treated with intravenous glucan (a yeast cell-wall extract) in an attempt to stimulate their monocyte-derived phagocytic cell system.

Baker[37] reported improvement of some psoriasis patients treated with nystatin, a drug that is not absorbed and that could be expected to have no effect other than on yeast in the gastrointestinal tract. At present, however, assessment of intestinal *Candida* carriage remains difficult and impractical for the dermatologist.

Candida albicans frequently is found in large numbers on dental plates of our psoriasis patients, and we believe this stimulus is sufficient to evoke a psoriatic response. The use of an ultrasonic cleaning tank seems useful in reducing the numbers of such yeast.[38]

Candida is sometimes recovered on culture from the throat and from fingernail folds. (Most body fold inverse psoriasis, in contrast, does not seem to be associated with *Candida*; more often the organisms found there are group B streptococci.)

Candida albicans is suspected on clinical grounds in palm and sole psoriasis (but not usually pustular psoriasis of the palms and soles) and also with a generalized psoriatic scaly erythroderma. Itching in psoriasis often suggests involvement with *Candida.* Nystatin,[39] sometimes in association with cholestyramine, is the usual treatment for suspected yeast-gastrointestinal-associated psoriasis.

In instances where such treatment seems to work for a while and then loses effect, fluconazole in doses of

100 or 200 mg/day has proved effective. In such cases, it seems more effective than ketoconazole; conversely, in instances when patients with seborrheic-distribution psoriasis developed elevated liver enzyme tests and had their treatment changed to fluconazole, there was clearly a loss of therapeutic effect. Schwartz et al[40] recently reported fluconazole's usefulness in treating human immunodeficiency virus-associated psoriasiform dermatitis.[40] Also, itraconazole appears to be effective in treating *Candida*-associated psoriasis, and the persistently high levels of the drug occurring in nails also may alleviate nail psoriasis.[41]

GROUP A BETA-HEMOLYTIC STREPTOCOCCI

The association of group A beta-hemolytic streptococci (GABHS) and psoriasis has been well documented in the literature. Furthermore, it is clear from those sources that the streptococcal-psoriasis association is not confined to guttate or childhood psoriasis; it also does not always accompany a clinically evident sore throat.

In 1916, Winfield[42] reported that patients with psoriasis often improved after tonsillectomy, and subsequent papers continued to document that. Cohen-Taervert and Esseveld[43] examined 135 patients with plaque-type psoriasis and found only 18% with clinical evidence of an upper respiratory tract infection but 34% with a positive throat culture.

In a study of microbiologic findings on 297 psoriasis patients, Noah[1] found evidence of GABHS in only nine. A frequent finding, however, was an elevation in one or more of the anti-group A extracellular enzyme levels. We consider either positive culture or an elevated level of serum antibody to streptococcal exoenzymes as evidence of streptococcal presence. Our present practice is to use a battery of four such antibody tests: antistreptolysin-O, antihyaluronidase, anti-DNase-B, and Streptozyme.

Most of the psoriasis patients in whom signs of streptococci are present do not have an obvious sore throat, infected tonsils, or give a history of recent streptococcal infection. In such patients, the streptococcal carrier state (presence of pathogenic organisms in the absence of clinical signs of infection) probably is responsible for the persistence of psoriatic activity.

Unfortunately, it is harder to eliminate the streptococcal carrier state[44] than it is to treat an acute streptococcal infection. The addition of rifampin to a course of penicillin or erythromycin increases the chance of success.[45] We[46] have reported an apparent benefit of such rifampin combinations in treating selected patients with psoriasis, but Vincent et al[47] could not demonstrate any such effect.

Belew[48] and Chalmers[49] have shown that there are no uniquely associated serotypes of streptococcus in psoriasis such as is found in rheumatic fever or glomerulonephritis. Both polyclonal and monoclonal immunofluorescent tagged antibodies to streptococci stain skin from subjects with suspected streptococcal-associated psoriasis.[50] Whether these findings are evidence of streptococcal fragments in psoriatic lesions or whether they merely represent cross-reactivity between skin and the streptococci[51] remains to be determined.

GROUP B BETA-HEMOLYTIC STREPTOCOCCI

Marples[52] pointed out that the two preferred sites for microbial life on the human skin are within the hair follicle and in the skin folds. Skin fold, so-called inverse, psoriasis is a familiar clinical variant, and involvement of the gluteal cleft is so frequent in psoriasis as to be almost a diagnostic sign. It turns out that the most important pathogen in such psoriasis is *Streptococcus agalactia* or group B-beta hemolytic streptococci (GBBHS). This organism frequently colonizes the vaginal mucosa and the perianal region and is also an important pathogen in bacterial meningitis in the neonate.

Its association with psoriasis has been described by Schacter et al[53] and Nobles[54] and was found in 110 affected skin sites by Noah.[1] An additional 11 isolates in these 297 patients were from the urine. Group B streptococci also have been recovered from nailfold skin in association with psoriatic arthritis of the terminal phalarynx.[1] Systemic ampicillin and topical erythromycin are the agents used most often in treating affected areas from which GBBHS is recovered. Like GABHS, there is no specific serotype of GBBHS associated with psoriasis.[55]

In some instances of resistant psoriasis of the glans penis, GBBHS from the vagina of these patients' sexual partners has been cultured; treatment of the female partner in some instances has appeared to be helpful.

ENTEROCOCCUS FAECALIS

This intestinal organism, formerly called *S faecalis* or group D beta-hemolytic streptococci, was found in 55 of the 297 cases of psoriasis surveyed by Noah.[1] Swartz[56] and later Robinson[57] demonstrated an intense reactivity to the injection of minute, skin test quantities of enterococcal vaccine in patients with psoriasis.

Enterococcus faecalis is notoriously hard to treat with antibiotics. In some instances, oral vancomycin, an agent that is not absorbed from the gastrointestinal tract, has seemed to helped patients with psoriasis, presumably by suppressing the growth of intestinal enterococci. Ofloxacin, a quinolone with anti-enterococcal activity that was subsequently removed from the market, also appeared to be helpful in treating some patients from whose skin folds *Enterococcus* had previously been cultured.

KLEBSIELLA

Klebsiella pneumoniae and *Klebsiella oxytoca,* gram-negative rods, frequently are cited as being of relevance by those who consider the closely associated spondyloarthritis a form of "reactive" arthritis. Noah[1] isolated the organism from the skin or throat in 26 of 297 psoriasis patients.

Klebsiella responds to treatment with a variety of antibiotics, including cephalexin. The possibility of *Klebsiella* involvement should be considered in older psoriasis patients who have some degree of congestive heart failure because *Klebsiella* often colonizes the respiratory tract of such patients.

PSEUDOMONAS AERUGINOSA

Noah[1] found *Pseudomonas* species in 20 instances in the 297 patients studied. *Pseudomonas* and an additional 23 isolations of related organisms such as *Acinetobacter* were observed in very ill psoriasis patients who had been treated previously with occlusive plastic suits over high-potency corticosteroid. *Pseudomonas* also has been associated with acute flares of psoriasis following exposure to *Pseudomonas*-contaminated hot tubs. *Pseudomonas* also has been found on the surface of a waterbed mattress of a patient with very severe and labile psoriasis and psoriatic arthritis. Removal of these fomites from the patient's environment along with appropriate therapy appeared to help the skin.

Successful treatment of *Pseudomonas* infection is never easy. Attention to the environment, topical gentamicin, and systemic ciprofloxacin and carbenicillin have proven to be the most useful.

PROTEUS MIRABILIS, E COLI, AND OTHER URINARY TRACT GRAM-NEGATIVE ROD PATHOGENS

Recurrent infection and persisting low-level colonization of the urogenital tract with pathogenic microbes are common in both men and women. When found, these infections ordinarily are easy to treat with antibiotics, and the beneficial effect on the patient's psoriasis is often dramatic.

Noah[1] found evidence of urinary tract gram-negative rods in 25 of 297 psoriasis patients. Those findings are based on the recovery of even small numbers of urinary tract pathogens on clean-catch urine specimens. Most medical laboratories will not report the presence of pathogens in numbers less than 100 000 per mL or in the presence of three or more potential pathogens, preferring to call those instances evidence of colonization rather than infection. We, however, consider this kind of colonization significant when it is found in patients predisposed to psoriasis. It is important to have a prior understanding with one's laboratory in order to receive identification reports of mixed infection or of less than 100 000 per mL colonization.

BACILLUS CEREUS

We have encountered a number of cases of impetigo-like psoriasis from which *B cereus* was recovered. In many of those instances the patient bathed or swam in unchlorinated well or pond water. Successful treatment of these cases has required not only antibiotic (usually topical and oral erythromycin) but also cessation of exposure to the potable but *Bacillus*-containing water source.

HELICOBACTER PYLORI

This "new" organism is only now being appreciated as a significant cause of gastritis and gastric and duodenal ulcers. Of particular interest is the fact that it can be suppressed but almost never eradicated following treatment with single-agent antibiotics. The use of what is termed "triple therapy" consisting of a combination of amoxicillin or doxycycline, metronidazole, and bismuth subsalicylate is often curative.

One of our patients whose psoriasis had cleared with amoxicillin treatment, only to shortly recur, told us he had active peptic ulcer disease that was being suppressed with rantidine. We then retreated him with "triple therapy." His skin cleared again, and this time has stayed relatively well, despite a continuing positive ELISA titer to *H pylori* antigen.

Schneider et al[58] found a positive ELISA titer to *H pylori* in 15 of 32 psoriasis patients compared with 46 of 94 of those with rosacea, 17 of 32 of those with dermatitis, and 5 of 14 of those with keratoses and other small, noninflammatory lesions.

CONCLUSIONS

What, then, are we to make of these findings of a

variety of bacteria and yeast in patients with psoriasis and their often gratifying but inconsistent response to antibiotic treatment? The relation of antecedent infection to flares of psoriasis is well established. The convention has been to term this an example of the Koebner phenomenon. We have addressed this at length[59] and disagree, but in any case most patients with psoriasis do not have an obvious infection, nor do they relate a history of recent infection. In fact, the old aphorism, "psoriasis is a disease of healthy people," seems to be accurate. Our experience has led us to conclude that otherwise apparently healthy psoriasis patients are often found to be harboring pathogenic microorganisms and that their psoriasis improves when they are treated with antibiotics.

Our present view is to consider "colonization" or "carriage" of pathogenic microorganisms the essential feature of active psoriasis. Remove these pathogens, and the psoriasis patient retains an inherited tendency to react, but exhibits no clinical evidence of either skin or joint disease.

Do antibiotics offer a practical way to manage psoriasis? In our experience, a search for relevant microbes and treatment with antimicrobial drugs is a practical way to manage psoriasis. Recently, we reported results of antimicrobial treatment of 126 patients with psoriasis, many of these problem cases referred by other physicians.[60] Approximately 50% of our patients were completely or almost completely cleared of their disease, another 30% markedly improved, and in about 20% the treatment failed. These results compare favorably with results achieved with other treatments including some with a substantial potential for harm. Certainly, we think that a work-up and therapeutic trial of antimicrobial treatment should always be attempted before starting treatment with methotrexate, etretinate or cyclosporin, and probably prior to the institution of psoralen-ultraviolet-light therapy. Even for patients who can control their disease topically with either corticosteroid or tars but who require almost continuous such applications, this kind of approach appears to offer significant potential benefit.

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